MACROSCOPIC ANALYSES OF THE EFFECTS OF HYALURONATES AND CORTICOSTEROIDS ON INDUCED OSTEOARTHRITIS IN RABBITS' KNEES

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ABSTRACT

Objective: To evaluate the effects of intra-articular injections of corticosteroids, native hyaluronic acid and branched-chain hyaluronic acid in experimentally-induced osteoarthrosis. Methods: 44 rabbits underwent anterior cruciate ligament resection and were then divided into four groups of eleven. Group 1: one intra-articular injection of saline solution per week, for three weeks; Group 2: three injections (one per week) of native hyaluronic acid; Group 3: three injections (one per week) of branched-chain hyaluronic acid; Group 4: two injections of betamethasone with an interval of three weeks. The cartilage of the tibial plateaus was evaluated macroscopically twelve weeks after surgery. Changes to the joint surface were graded as follows: Grade 0: smooth joint surface without relief changes; Grade 1: rough surface without any depressions; Grade 2: similar to grade 1, but with depressions on the joint surface; and Grade 3: subchondral bone exposure. The statistical analysis consisted of the use of Student's t test, chi-square test and analysis of variance (ANOVA). The significance level used was 5%. Results: A statistical difference was found between the control group and the three study groups (2, 3 and 4) in relation to the development and severity of arthrosis. However, there was no difference between the groups regarding the drugs studied. Conclusion: A similar degree of attenuation of the osteoarthrosis process in the rabbits' knees was found with the use of intra-articular injections of low-molecular-weight and high-molecular-weight glycosaminoglycans, and the corticosteroid betamethasone, compared with placebo.

Keywords – *Hyaluronic acid. Anterior cruciate ligament; Osteoarthritis; Knee; Rabbits*

INTRODUCTION

Osteoarthrosis is the most common joint disease among the elderly population. Its prevalence is greater than 10% among individuals over the age of 50 years and it may cause significant functional limitations[1,2]. Among the different types of treatment available today, therapy with intra-articular injections of hyaluronic acid has shown beneficial effects in relation to controlling the symptoms of gonarthrosis[3].

Hyaluronic acid, which is a polysaccharide in the glycosaminoglycan family, contributes towards homeostasis in normal joints and presents lower concentrations and diminished molecular weight in the synovial fluid of joints with osteoarthrosis[4-6]. When administered in the form of intra-articular injections, hyaluronic acid may increase the power of the regenerative effects of endogenous hyaluronic acid on the joint cartilage, by restoring the viscoelasticity of the synovial fluid, contributing towards synthesis of hyaluronic acid by synoviocytes and preventing degradation of proteoglycans and collagen fibers in the extracellular matrix. It stimulates the metabolism, prevents apoptosis of chondrocytes and inhibits chondral degradation and inflammatory responses in

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the joints[6]. These therapeutic effects from hyaluronic acid are attributed not only to its capacity to ease the symptoms relating to osteoarthrosis, but also to its interference with the progression of joint degeneration[4,5].

Another therapeutic option for managing gonarthrosis is intra-articular injections of corticosteroids. Clinical studies have shown favorable results with regard to pain relief and functional improvement following intra-articular injections of betamethasone disodium phosphate, betamethasone acetate or methylprednisolone[7,8]. Intra-articular administration of corticosteroids at low to moderate doses may reduce the progression of cartilage erosion and the formation of osteophytes[9]. In addition to suppressing the production of metalloproteinases, which have been implicated in the genesis of osteoarthrosis, it has the capacity to partially prevent destruction of cells and tissues of the cartilaginous matrix by oxygen free radicals[10,11].

In view of the widespread occurrence and implications of knee osteoarthrosis, the importance of diagnosing and treating it at its initial stages, in order to minimize its consequences, is now understood[12]. Because no interventions capable of inhibiting its evolution are currently available, what remain are options that allow its progression to be reduced. Intra-articular injections of different types of hyaluronic acid and corticosteroids may be used for this purpose.

To evaluate the effects of these substances on gonarthrosis, it was proposed in this investigation to use an experimental model for osteoarthrosis that would resemble what is observed in humans. Sectioning of the anterior cruciate ligament of rabbits' knees mimics the morphological and biochemical changes that are observed in human osteoarthrosis, which enables accurate reproduction of the results obtained[13-14].

The aim in this study was to evaluate the effect of intra-articular injections of native hyaluronic acid (Polireumin®, TRB Pharma, São Paulo, Brazil), branched-chain hyaluronic acid (Synvisc®, Novartis, São Paulo, Brazil) and the corticosteroid betamethasone (Diprospan®, Schering-Plough, São Paulo, Brazil), separately and in comparison with each other, in osteoarthrosis induced by sectioning the anterior cruciate ligament in rabbits' knees.

METHODS

Forty-four male rabbits of the California breed were used. They were kept housed in cages (two animals per cage) in a vivarium, before and while performing the procedures. They received standard feed and had free access to water. The lighting conditions were controlled, with light-dark cycles of 12 hours each, and the temperature (22 ± 1ºC), humidity and noise levels were kept stable. These conditions were maintained until the rabbits reached a mean weight of 3.5 kg.

All the animals firstly underwent resection of the anterior cruciate ligament.

The surgical procedure consisted of preoperative anesthesia using 10 mg/kg of ketamine hydrochloride (Dopalen®) and 50 mg/kg of xylazine hydrochloride (Anasedan®), administered in the same syringe, intramuscularly into the belly of the semimembranosus and semitendinosus muscles of the right hind leg. On the same occasion, injections of 14,400 IU of penicillin and 6 mg of streptomycin (Pentabiótico Veterinário Reforçado® - Eurofarma) were administered as antibiotic prophylaxis, and Flunamine® (Bayer), at a dose of 2.2 mg/kg intramuscularly, was administered for postoperative analgesia.

The right knee was shaved and antisepsis consisting of polyvinylpyrrolidone (Povidone®) was applied. After setting up sterile fields, a medial parapatellar incision was made in the skin and subcutaneous tissue, followed by capsulotomy and lateral luxation of the patella.

The knee was then positioned at maximum flexion, which allowed the anterior cruciate ligament to be viewed. This was sectioned using a no. 15 scalpel blade, the joint was irrigated with isotonic saline solution and then capsulorrhaphy and skin suturing were performed using 4-0 mononylon (Figure 1).

The rabbits continued to be housed in their respective cages after the operation, without restriction on placing weight on the operated leg. They were distributed randomly into four groups of 11 animals each. Three weeks after the surgical procedure, the respective intra-articular injections were started.

Group 1: control, injections of isotonic saline solution at one-week intervals, for three weeks.

Group 2: three infiltrations at one-week intervals, using native hyaluronic acid (Polireumin®).

Group 3: three infiltrations at one-week intervals, using branched-chain hyaluronic acid (Synvisc®).

Group 4: two infiltrations separated by a three-week interval, using betamethasone 0.25 mg as the dipropionate and 0.1 mg as the phosphate (Diprospan®).

One rabbit in group 2 and another in group 3 evolved

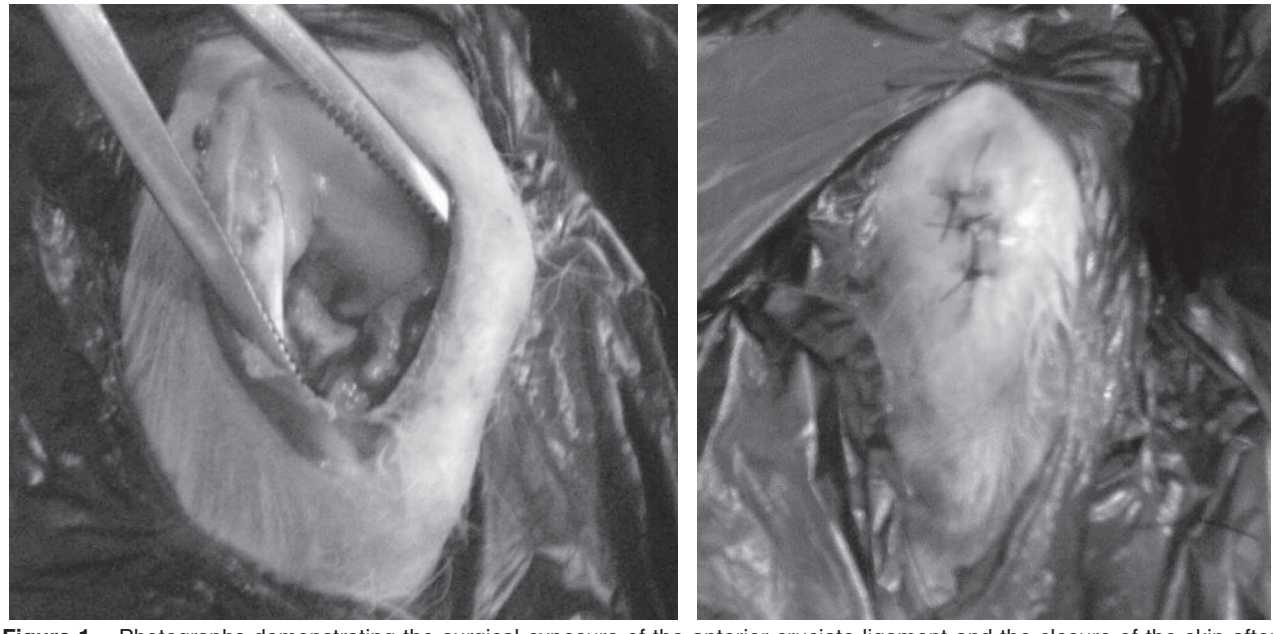

Figure 1 – Photographs demonstrating the surgical exposure of the anterior cruciate ligament and the closure of the skin after the resection

with infection of the operative site that extended to the joint, and were excluded from the study.

The rabbits were killed 12 weeks after the operation. For this, they were firstly anesthetized as described above and then subjected to intracardiac injection of thiopental (5 ml) and potassium chloride (10 ml).

The tibial plateaus were resected aseptically, and were immersed in a flask containing 10% formol, for subsequent macroscopic evaluation of the joint cartilage.

The changes to the joint surface were graded macroscopically as follows: grade 0 – smooth and shiny joint surface, without abnormalities of relief; grade 1 – rough surface, with loss of shininess, without depressions; grade 2 – similar to grade 1, with depressions on the surface; grade 3 – exposure of the subchondral bone (Figure 2). The lateral and medial tibial plateaus were evaluated separately in each group.

The statistical analysis consisted of using Student's t test to determine whether there were any differences between the different groups in relation to the degrees of osteoarthrosis, viewed macroscopically. To determine whether there were any internal differences in the groups regarding the degree of osteoarthrosis in the lateral and medial compartments, the chi-square test was performed. To investigate differences between the degrees of osteoarthrosis, independent of the drug used, analysis of variance (Anova) was used.

RESULTS

Osteoarthrosis induced by resection of the anterior cruciate ligament occurred in the placebo group in both compartments in all the knees. In groups 2, 3 and 4, it occurred in 40%, 65% and 45% of the compartments, respectively (Table 1 and Figure 3).

Table 1 – Frequencies of the different degrees of osteoarthrosis in the medial and lateral compartments of the study groups

Disease grade	placebo	%	Polireumin	%	Synvisc	%	corticoid	%
G0	0	0.00	12	60.00	7	35.00	12	54.54
G1	13	59.09	1	5.00	7	35.00	7	31.82
G2	5	22.73	7	35.00	6	30.00	3	13.64
G3	4	18.18	0	0.00	0	0.00	0	0.00
Total	22	100.00	20	100.00	20	100.00	22	100.00

The significance level used for all the analyses was 5%.

Student's t test was used to compare the different drugs and the placebo, regarding the development of osteoarthrosis. A statistical difference was observed between each of the groups 2, 3 and 4 and the control group (Table 2), but there were no differences among the drug groups, taking $p < 0.05$.

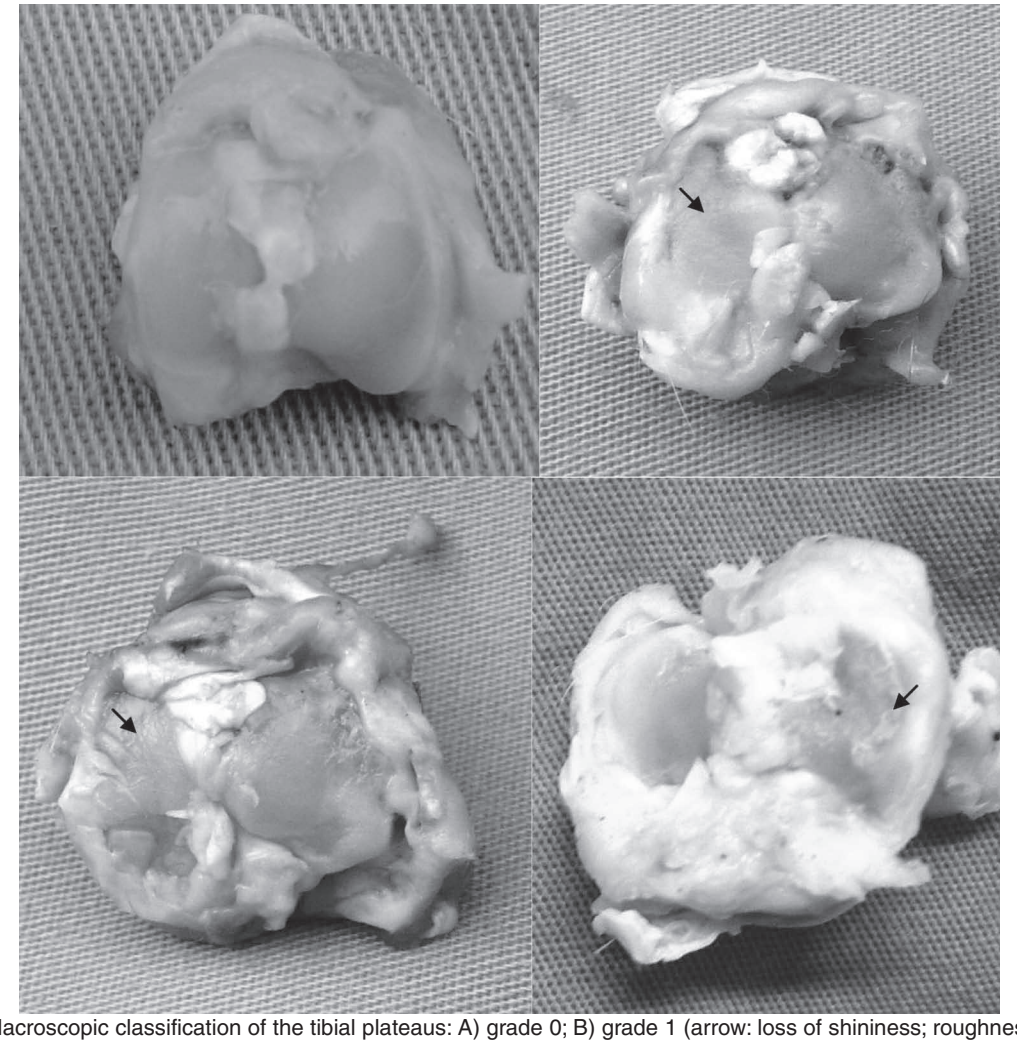

Figure 2 – Macroscopic classification of the tibial plateaus: A) grade 0; B) grade 1 (arrow: loss of shininess; roughness); C) grade 2 (arrow: surface depression); D) grade 3 (arrow: exposure of subchondral bone)

Table 2 – Student's t test

Drugs	Calculated t
Synvisc/ corticoid	0.8232
Synvisc/ Polireumin	1.0000
Corticoid/ Polireumin	0.8790

The critical t value for all the comparisons was 2.7764
Significance level of 5%

Through Anova, it was seen that there was a difference between different degrees of osteoarthrosis, independent of the drug used (Table 3).

Table 3 – Variance test (Anova)

Source of variance	F	P value
Disease grade	6.5890	0.025

Comparison of the degree of osteoarthrosis within each group, between the medial and lateral compartments, showed that there was no significant difference in any of the study groups, according to the chi-square test (Table 4).

Table 4 – Chi-square test

Drugs	calculated
placebo	0.8707
Synvisc	0.0631
corticoid	0.1066
Polireumin	0.0040

Chi-square value tabulated with significance of 0.05 and one degree of freedom was 3.84

DISCUSSION

In this experiment, the joint cartilage of the medial and lateral tibial plateaus of the rabbits' knees that were subjected to sectioning of the anterior cruciate ligament and to infiltrations of hyaluronates, corticosteroid and isotonic saline solution (control) were evaluated macroscopically. The definitions of the different degrees of osteoarthrosis were based on observations of the appearance of the joint cartilage surface, going from normal (grade 0) to complete destruction of the cartilage and exposure of the subchondral bone (grade 3). Based on this classification, it was observed that, in all the knees infiltrated with isotonic saline solution, there was some degree of chondral lesion and severe joint degeneration (grade 3) in 18%. In the other groups, there were cases that did not evolve to arthrosis, and the maximum that was observed was changes to the joint surface relief (Table 1 and Figure 3).

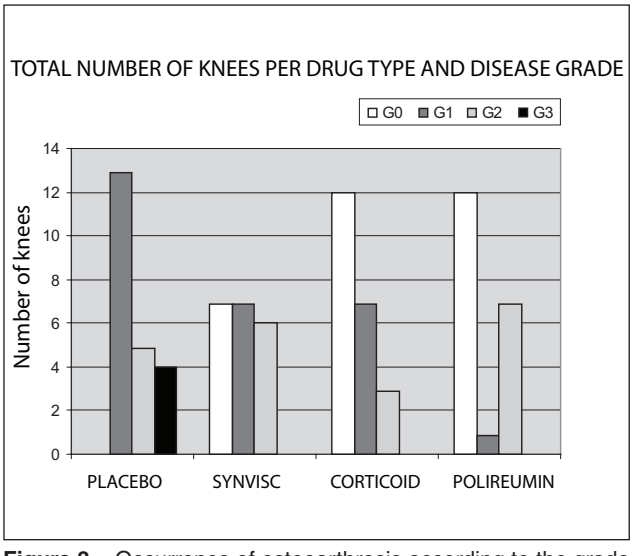

Figure 3 – Occurrence of osteoarthrosis according to the grade in the tibial plateaus in the different groups

The results demonstrated that there was a statistical difference with regard to prevention of chondral lesions, between the placebo group and the groups that received joint injections of different types of hyaluronic acid or corticosteroid (Table 2). There was no predominance of joint lesions between the lateral and medial tibial compartments in any of the groups (Table 4). In the same way as shown by other studies in the literature, the present study demonstrated that the intra-articular injections of low and high molecular weight glycosaminoglycans and corticosteroid had a protective effect on the chondral bone[5,15-18]. This is also in agreement with the study by Karakurum *et al*[8], who compared intra-articular injections of prednisolone with injections of hyaluronic acid, in an experimental osteoarthrosis model in rabbits, and observed that the two drugs administered separately prevented joint degeneration to the same extent, while the effect was boosted when the drugs were administered together.

For the infiltrations with corticosteroids, doses proportional to those of human treatments were used, thereby avoiding worsening of the chondral lesions due to excess medication. The protective effect on chondral bone that has been observed in different studies occurred with the use of corticosteroids in low doses. The three-week interval between the applications of corticosteroid was used because corticosteroids are less soluble and may remain inside the joint for this period[19].

Yoshimi *et al*[4] developed the osteoarthrosis model involving sectioning the anterior cruciate ligament in rabbits' knees. In comparison with other models, such as partial medial meniscectomy in rabbits and sectioning the anterior cruciate ligament in dogs or rats, their model is the one that comes closest to the joint degeneration process in humans[20-25]. Published studies in the literature that used this model to evaluate the protective effect on chondral bone of glycosaminoglycans and corticosteroids have mostly demonstrated that the control groups develop arthrosis[4,5,8-10,14,15,24-26]. However, contrary to experimental studies, recent randomized prospective clinical trials have not proven the protective effect on chondral bone of different types of hyaluronic acid and corticosteroid. What is presented as evidence is the improvement in pain levels and functional ability regarding activities of daily living among patients who made use of these medications over short periods[27-38]. Controlled studies with longer follow-up periods are needed in order to clarify the role of these drugs in prevention of degeneration of the joint cartilage.

In a continuation of this investigation, it is intended to use histological analysis and histomorphometric quantification of glycosaminoglycans in the extracellular matrix to assess the influence of these substances on the osteoarthrosis model used here.

CONCLUSION

From the present study, it is concluded that attenuation of the process of osteoarthrosis takes place to the same extent through the use of intra-articular injections of low molecular weight glycosaminoglycans, high molecular weight glycosaminoglycans and corticosteroid composed of betamethasone dipropionate and betamethasone disodium phosphate, in rabbits' knees.

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